Received: 22 October 2018 | Accepted: 18 January 2019

DOI: 10.1111/aogs.13553

SYSTEMATIC REVIEW

Management of women with atypical polypoid adenomyoma of the uterus: A quantitative systematic review

Antonio Raffone[1] | Antonio Travaglino[2] | Gabriele Saccone[1] | Carlo Alviggi[1] | Massimo Mascolo[2] | Giuseppe De Placido[1] | Luigi Insabato[2] | Antonio Mollo[1] | Fulvio Zullo[1]

[1]Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

[2]Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy

Correspondence
Antonio Travaglino, Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy.
Email: antonio.travaglino.ap@gmail.com

Abstract

Introduction: Atypical polypoid adenomyoma is an uncommon uterine lesion which can coexist with endometrial atypical hyperplasia and/or cancer. Atypical polypoid adenomyoma affects premenopausal women in most cases, but it shows high recurrence rate if conservatively treated. To date, the management of patients is based on low-quality evidence and is not standardized. Our primary aim was to explore the optimal management of atypical polypoid adenomyoma, with particular regard to the fertility-sparing approach. The secondary aim was to define clinicopathologic features of atypical polypoid adenomyoma.

Material and methods: Medline, Embase, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, Google Scholar and Cochrane Library were searched for studies reporting outcomes of atypical polypoid adenomyoma treatments. Univariate comparisons among outcomes of fertility-sparing treatments (rates of initial response, progression, recurrence, final complete response, pregnancy) were performed with Fisher's exact test ($\alpha = .05$).

Results: Eleven retrospective studies with 237 patients were included; 85.5% of patients were premenopausal and 62.9% were nulliparous. Atypical polypoid adenomyoma coexisted with atypical hyperplasia in 5.5% of cases and with endometrial cancer in 5.9%. Overall risks of recurrence and progression to cancer were 28.9% and 16.6%, respectively. Fertility-sparing treatments included hormonal therapy with or without maintenance, hysteroscopic transcervical resection, dilation and curettage, and hormonal therapy combined with transcervical resection or dilation and curettage. Transcervical resection showed significantly higher initial response rates (P from <.001 to .023) than any other treatment. Transcervical resection and transcervical resection+hormonal therapy showed significantly lower progression rates ($P < .001$), and higher final complete response rates ($P < .001$) than any other treatment. No significant differences were found in the rates of pregnancy ($P = .533$-$.647$) or recurrence ($P = .052$-$.475$). Among the different transcervical resection techniques, the 4-step transcervical resection showed significantly lower rates of

Abbreviations: APA, atypical polypoid adenomyoma; BMI, body mass index; D&C, dilation and curettage; HBSO, hysterectomy and bilateral salpingo-oophorectomy; HT, hormonal therapy; M, maintenance; TCR, transcervical resection.

progression (P = .002) and recurrence (P = .013) than other techniques. Limitations to our results were the retrospective design of the studies and the relatively small sample size, due to the rarity of atypical polypoid adenomyoma.

Conclusions: Based on its effectiveness and safety, transcervical resection may be the first-line fertility-sparing treatment for atypical polypoid adenomyoma. In particular, 4-step transcervical resection showed the best results. Given the risk of recurrence, progression and coexistent atypical hyperplasia or cancer, follow-up biopsies are advisable. When fertility preservation is not required, hysterectomy might be advisable.

KEYWORDS

atypical polypoid adenomyofibroma, conservative treatment, endometrium, hysteroscopy, progestin, transcervical resection

1 | INTRODUCTION

Atypical polypoid adenomyoma or atypical polypoid adenomyofibroma of the uterus (APA) is an uncommon uterine lesion, first described by Mazur in 1981.[1] Histologically, it is a biphasic proliferation, which consists of atypical endometrial glands with squamous morular differentiation in a background of profuse myofibromatous stroma.[2] Its histological pattern mimics adenocarcinoma infiltrating myometrium, or malignant mixed mullerian tumor.[1]

Although APA is considered as a benign tumor, it can coexist with endometrial atypical hyperplasia and/or endometrioid adenocarcinoma.[3] Moreover, APA shows high recurrence rates when conservatively treated.[3,4] Therefore, hysterectomy has been considered as the treatment of choice for this lesion.[4]

However, since APA affects premenopausal women in most cases,[5-7] a fertility-sparing approach appears necessary. Several conservative treatments have been adopted, including progestin-based hormonal therapy (HT) with or without maintenance (M), hysteroscopic transcervical resection (TCR), dilation and curettage (D&C) or the combination of HT with TCR or D&C.[1,5-14]

Given the rarity of APA, no prospective trials have been performed, and the management of patients has never been standardized. As a result, there is no consensus on the optimal treatment and follow up of APA.

In fact, several clinicopathologic features of APA, such as characteristics of the patients, symptoms, associations with other diseases, localization in the uterus, actual risk of recurrence, malignant progression and coexistence with endometrial atypical hyperplasia and/or cancer, are not well-defined.

The objective of this quantitative systematic review was to provide a comprehensive and updated overview about all aspects of this rare uterine lesion. In particular, our primary aim was to compare effectiveness and safety of the several conservative treatments described in the literature. We aimed to provide statistical evidence to support the standardization of the patient management.

Key message

Transcervical resection should be the first-line fertility-sparing treatment for atypical polypoid adenomyoma. In particular, the 4-step resection technique might be an optimal approach. Follow-up biopsies appear necessary, and hysterectomy might be advisable when fertility preservation is not required.

2 | MATERIAL AND METHODS

This study was performed following a protocol recommended for systematic review. The protocol defining methods for collecting, extracting and analyzing data was designed a priori. All steps were conducted independently by two reviewers (A.R., A.T.). These two authors independently performed electronic search, evaluation of eligibility of the studies, risks of bias assessment, data extraction and data analysis. Disagreements were resolved by discussion with a third reviewer (G.S.).

The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[15]

2.1 | Search strategy

Several researches were performed using MEDLINE, Embase, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, Google Scholar and Cochrane Library as electronic databases. The relevant articles were searched from the inception to May 2018 using a combination of the following text words and all their synonyms found on Medical SubHeading (MeSH) vocabulary: “atypical polypoid adenomyoma”; “APA”; “adenofibroma”; “adenomyofibroma”; “uterus”; “uterine”; “endometrial”; “myometrium”; “treatment”; “fertility-sparing”; “conservative”; “MPA”; “medroxyprogesterone”; “LNG-IUD”; “Mirena”; “levonorgestrel”; “progesterone”; “progestogen”; “progestin”;

"response"; "resistance"; "persistence"; "relapse"; "recurrence"; "progression"; "outcome"; "precancerous"; "premalignant"; "precursor". In addition, reference lists of relevant studies were reviewed.

2.2 | Study selection

All peer-reviewed, prospective or retrospective studies reporting a series of patients with APA who underwent any type of treatment were included in the systematic review.

Exclusion criteria were:

- studies not reporting the treatment;
- studies not reporting outcomes of treatment;
- case reports and reviews.

2.3 | Data extraction

Data from each eligible study were extracted without modification of original data according to PICOS.

Population (P) of our study was constituted of women diagnosed with APA.

Interventions (I) included all treatments performed for APA. Treatments of APA were subdivided into conservative and non-conservative. Conservative treatments included TCR, HT, HT+M, D&C, vaginal resection, or a combination of TCR or D&C with HT. Non-conservative treatments included simple hysterectomy or hysterectomy plus bilateral salpingo-oophorectomy (HBSO).

Comparisons (C) were performed among conservative treatments (see data analysis).

Outcomes (O) of the conservative treatments were subdivided into oncologic and reproductive outcomes.

Oncologic outcomes considered were the following:

- initial response, defined as regression of APA on histological examination at 6 months-follow up;
- recurrence, defined as a new finding of APA on follow-up biopsy after a complete regression; multiple recurrences were consecutively numbered;
- final complete response, defined as complete regression of APA at the end of the follow-up period;
- progression, defined as progression of APA to endometrial endometrioid adenocarcinoma;
- disease-free interval, defined as the time between complete response and recurrence.

Additional oncologic outcomes were:

- persistence, defined as the presence of APA on histological examination at 6 months-follow up;
- final hysterectomy, defined as hysterectomy after a failed conservative treatment (due to progression to cancer or association with endometrial atypical hyperplasia);
- time to hysterectomy, defined as the time in months between the beginning of the conservative treatment and hysterectomy after the failure of treatment.

Reproductive outcomes were defined as pregnancies after a conservative approach.

Study design (S) was retrospective case series (the only possible design given the rarity of APA).

2.4 | Risk of bias assessment

The risk of bias was assessed via the Methodological Index for Non-Randomized Studies (MINORS).[16] Seven domains related to risk of bias were evaluated in each study: (1) aim (ie, clearly stated aim); (2) inclusion of consecutive patients (ie, all patients satisfying the criteria for inclusion were included in the study during the study period); (3) prospective collection of data (ie, data were collected according to a protocol established before the beginning of the study); (4) endpoints appropriate to the aim (ie, unambiguous explanation of the criteria used to measure outcomes); (5) unbiased assessment of the study endpoint (ie, the study endpoint was assessed without bias); (6) follow-up period appropriate to the aim (ie, the follow up was sufficiently long to allow the assessment of the main endpoint), (7) loss to follow up less than 5% (ie, no more than 5% of patients were lost to follow up). Review authors' judgments were categorized as "low risk", "unclear risk" or "high risk" of bias if data regarding the domain were "reported and adequate", "reported but inadequate" or "not reported", respectively.

2.5 | Data analysis

Univariate comparisons among conservative treatments and among different TCR techniques were performed using Fisher's exact test for a two-tailed *P*-value with $\alpha = .05$ significance level for each oncologic or reproductive outcome. Meta-analysis was not feasible due to the absence of comparison among the conservative approaches in the individual studies.

Studies with overlapping data were considered as one study in the data analysis.

The data analysis was performed using REVIEW MANAGER 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

3 | RESULTS

3.1 | Study selection

In all, 333 studies were identified through database searching. 103 articles remained after duplicate removal, of which 90 were considered relevant and were screened. Thirteen studies were assessed for eligibility; after applying exclusion criteria, two of them were excluded. The last 11 retrospective studies with a total of 237 APA were included in the quantitative systematic review.[1,5-14] Two of the included studies[8,9]

reported overlapping data and were considered as one study in the data analysis.

Details about the whole process of study selection are reported in Supporting Information Figure S1.

3.2 | Risk of bias assessment

Results of risk of bias assessment are shown in Supporting Information Figure S2.

For the "aim", "inclusion of consecutive patients" and "prospective collection of data" domains, all the included studies were classified as low risk of bias, since they had a clearly stated aim, included consecutively all eligible patients, and collected data according to a previously defined protocol, respectively.

For the "endpoints appropriate to the aim" domain, three studies[5,10,14] were classified as unclear risk of bias because they did not assess reproductive outcomes, ans one[11] was categorized as high risk since it assessed recurrence as the only outcome of treatment. Other studies were as low risk of bias because they evaluated both oncologic and reproductive outcomes.

For the "unbiased assessment of the study endpoint" domain, five studies were categorized as low risk of bias since they performed histological examination at every follow-up visit.[5,8-10,13] Six studies were classified as unclear risk because they performed histological examination only when ultrasonographic findings were suspicious, or if they did not specify whether histological examination was performed at every follow-up visit.[1,6,7,11,12,14]

For the "follow-up period appropriate to the aim" domain, all the included studies were classified as low risk of bias because the follow-up period they considered was long enough to assess the main endpoints.

For the "loss to follow up less <5%" domain, nine studies were categorized as low risk of bias, whereas two were classified as unclear risk because more than 5% of patients (18.5% and 5.7%)[5,7]

3.3 | Characteristics of patients

Patient age ranged between 17 and 73 years; body mass index (BMI) was between 16.6 and 28.7 kg/m^2; 85.5% of women were premenopausal and 62.9% were nulliparous; 35.4% had menstrual cycle irregularity and 18.6% were infertile. The most common symptoms were: abnormal uterine bleeding (28%), menorrhagia (19.8%), hypermenorrhea (18.7%), dysmenorrhea (4.9%), metrorrhagia (3.8%), secondary anemia (2.2%), vaginal discharge (1.1%), mass in the uterine cavity (1.1%), vaginal bleeding (.5%), menostaxis (.5%) and amenorrhea (.5%). Only 2.2% were asymptomatic. Uterine leiomyoma was the most commonly associated pathology (10.9%).

Details about characteristics of patients are reported in Table 1.

3.4 | Characteristics of APA

APA was diagnosed in 59.4% on histological examination of D&C specimen, 32.1% on hysteroscopic biopsies, 5.5% on hysterectomy for other indications, 1.8% on cervical polypectomy specimen and 1.2% on HBSO for other indications.

Atypical polypoid adenomyoma localization was uterine fundus in 55.8% of cases, lower segment of the uterus in 32.7% and uterine cervix in 11.5%. APA diameter ranged between 1 and 70 mm; the weight of the resected lesion was reported only in one study and ranged between .5 and 25 g with a mean of 4 g.[7]

On histological examination, the most common pathologies associated with APA were: adenomyosis (20.7%), endometrial cancer (5.9%), atypical endometrial hyperplasia (5.5%), endometrial hyperplasia without atypia (3.8%) and ovarian cancer (2.1%).

Characteristics of APA are reported in detail in Table 2.

3.5 | Non-conservative treatments

A total of 58 patients were non-conservatively treated. Fourteen (24.1%) women underwent simple hysterectomy (in 9 cases for other indications), 7 (12%) HBSO (in 2 cases for other indications), 3 (5.2%) primary cytoreductive surgery, 1 (1.7%) chemotherapy for coexisting cancer, 1 (1.7%) hysterectomy + radiotherapy for misinterpretation as a carcinoma, 1 (1.7%) HBSO + radiotherapy for misinterpretation as a carcinoma, and 1 (1.7%) hysterectomy + chemotherapy for misinterpretation as a carcinosarcoma.

3.6 | Conservative treatments

A total of 169 patients were conservatively treated: 91 (53.8%) women underwent TCR, 39 (23.1%) TCR+HT, 18 (10.7%) HT (of whom 5 with M), 17 (10.1%) D&C, 2 (1.2%) D&C+HT, and 2 (1.2%) vaginal resection. Three studies described in detail on the TCR technique adopted.[7,12,14] TCR techniques were: 4-step TCR according to Di Spiezio Sardo et al in the study by Ma et al,[14]step TCR + intrauterine device insertion (to prevent adherences) in the study by Chiyoda et al,[7] and TCR + curettage in the study by Grimbizis et al.[12]

3.7 | Follow-up of conservative approach

In three studies, the follow up of patients conservatively treated was based on D&C or hysteroscopic biopsy and transvaginal ultrasonography every 3-6 months.[8,9,13] In three other studies, hysteroscopic biopsy were performed only when ultrasonographic findings were suspicious.[7,12,14] In two studies the follow up was based on D&C without specifying the interval between each D&C.[5,10] Three studies [1,6,11] did not report details about follow up. The follow-up time ranged between 1 and 276 months. CA125 and CA19.9 were assessed in only one study, showing normal values.[7]

Details about treatments and follow up are shown in Table 3.

3.8 | Oncologic outcomes of conservative treatments

Combining all conservative treatments, initial response occurred in 86% of patients, progression in 16.6%, recurrence in 28.9% with a

disease-free interval ranging between 1 and 60 months, and final complete response in 69.9%. No death from APA was reported.

Initial response was significantly more common in TCR (98.7%) than HT (77.7%; $P = .004$), TCR+HT (69.2%; $P < .001$) or D&C (75%; $P = .023$).

The rate of progression to cancer did not significantly differ between TCR (10.8%) and TCR+HT (5.1%; $P = .49$), but TCR and TCR+HT showed significantly fewer progressions than HT without M (69.2%; $P < .001$).

No significant differences in the recurrence rates were found between TCR+HT (17.9%) and TCR (29.8%; $P = .191$), D&C (36.4%; $P = .475$) or HT without M (44.4%; $P = .052$).

Concerning final complete response rates, no significant differences were found between TCR (77.3%) and TCR+HT (82.1%; $P = .634$), but both approaches showed significantly higher rates than HT without M (15.4%; $P < .001$).

Due to the low number of patients, D&C and HT+M could not be compared with other conservative approaches regarding final complete response, final hysterectomy or progression. For the same reason, oncologic outcomes of D&C+HT could not be compared with those of other treatments.

Results on oncologic outcomes of the several treatments are reported in detail in Table 4; details about recurrent APA are shown in Table S1; additional oncologic outcomes are reported in Table 4.

3.9 | Reproductive outcomes of conservative treatments

Pregnancy was achieved in 25.3% of all patients who underwent conservative treatment. No significant differences in the pregnancy rates were found between HT with M (40%) and TCR+HT (30.8%; $P = .647$), TCR (21.1%; $P = .575$), HT without M (15.4%; $P = .533$).

Reproductive outcomes were not reported for D&C and D&C+HT. Two studies also reported pregnancies after recurrence.[6,7] Two patients conceived two times after treatment with HT or TCR+HT.[8,13]

Reproductive outcomes are detailed in Table 5.

3.10 | Comparison among TCR techniques

The 4-step technique showed the best results (100% initial response, 83.3% final complete response, 10% recurrence, 0% progression).[14] The 4-step TCR showed significantly lower progression and recurrence rates than 1-step TCR+ intrauterine device[7] ($P = .002$ and $P = .013$, respectively). No significant differences were found between 4-step TCR and TCR + curettage.[12] No significant differences were found for any other outcomes.

Details about outcomes of different TCR techniques are shown in Table 6.

4 | DISCUSSION

We found that TCR obtained a significantly higher initial response rate than any other conservative treatment. TCR and TCR+HT showed higher final complete response rate and lower progression rate than HT without M. No significant differences were found among the several conservative approaches regarding recurrence and pregnancy rates. Among the different TCR techniques, the 4-step TCR performed in the study by Ma et al[14] showed the best outcomes. The risk of recurrence (29.8%) and progression (10.8%) was high even after TCR.

Many case reports of APA were published in the literature, but only a few large patient series were available. Therefore, clinicopathologic characteristics of APA are not well-defined.

Despite a wide age range (17-73), we found that most women were premenopausal (85%) and nulliparous (62.9%), emphasizing the importance of an effective and safe fertility-sparing treatment. Regarding symptom presentation, APA was rarely an incidental finding. Amenorrhea was present in only one case,[7] whereas most patients showed abnormal uterine bleeding (28%). For this reason, most APA was diagnosed on histological examination of D&C (59.4%) or hysteroscopic specimen (32.1%). APA was more commonly localized in the uterine fundus (55.8%), contrary to what was previously reported (lower uterine segment)[4]; however, it should be underlined that we included only studies reporting outcomes of treatment, and some studies did not report localization (Table 2).

It appears crucial to quantify the actual risk of coexistent endometrial atypical hyperplasia or endometrioid adenocarcinoma when a conservative approach is considered. According to the 2014 WHO classification, atypical hyperplasia (endometrioid intraepithelial neoplasia) is the precursor of endometrioid adenocarcinoma and is differentiated from hyperplasia without atypia (a benign proliferation) based on the presence of cytological atypia.[17] We found that APA was associated with atypical hyperplasia in 5.5% of the patients and with endometrial cancer in 5.9%. These risks appear lower than those previously reported in the literature (8.8% for atypical hyperplasia and 8.8% for cancer).[3] It cannot be excluded that the lower risk of atypical hyperplasia may also depend on changes in the WHO classification. Anyway, the risk of coexistent cancer is by far lower than that observed in atypical hyperplasia, which is usually treated conservatively in fertile women.[17] These findings support the feasibility of the conservative treatment in fertile women.

To date, there is no standard management of APA. There is no consensus about the optimal treatment (conservative or non-conservative; type of conservative treatment) or follow up (modality and timing).

Based on the risk of recurrence (29.8%) and progression (10.8%) even after TCR, hysterectomy might be advisable as a first choice treatment. However, such management does not appear suitable for patients desiring pregnancy.

Considering that most patients were premenopausal (85.9%) and nulliparous (62.9%), a fertility-sparing treatment appears necessary. Several conservative approaches were described in the literature, but it is unclear which one should be preferred.

In our study, initial response, final complete response and pregnancy rates were used to estimate the effectiveness of the conservative

TABLE 1 Patient characteristics

Study (Ref)	Country	Design	Sample size	Study period	Patient selection	Patients	
						Age years, mean (range)	BMI kg/m^2, mean (range)
Nomura et al[9]	Japan	Retrospective	18	2001-2011	Consecutive	33.6 (26-45)	21.9 (18.3-27.6)
Ma et al[14]	China	Retrospective	43	2012-2016	Consecutive	56 (17-71)	-
Chiyoda et al[7]	Japan	Retrospective	35	2003-2015	Consecutive	35 (23-43)	20.8 (16.6-28.7)
Chen et al[13]	China	Retrospective	10	2004-2016	Consecutive	30 (23-40)	-
Grimbizis et al[12]	Greece	Retrospective	9	1998-2016	Consecutive	37.9 (29.6-46.2)	-
Nomura et al[8]	Japan	Retrospective	18	2001-2011	Consecutive	33.6 (26-45)	21.9 (18.3-27.6)
Matsumoto et al[11]	Japan	Retrospective	29	1985-2005	Consecutive	38 (22-58)	23.2 ± 6.2 SD
Longacre et al[6]	USA	Retrospective	55	-	Consecutive	39.9 (25-73)	31 obese patients (56.4)
Fukunaga et al[10]	Japan	Retrospective	6	1991-1994	Consecutive	33 (22-48)	-
Young et al[5]	USA	Retrospective	27	-	Consecutive	39.7 (21-53)	-
Mazur[1]	USA	Retrospective	5	-	Consecutive	38 (33-44)	-
Total			237			- (17-73)	- (16.6-28.7)

-, not reported.

treatments, and progression and recurrence rates were used to define the safety.

According to our results, TCR (not followed by HT) appeared to be better than any other conservative treatments of APA. At an overall evaluation, TCR alone appeared an effective and safe fertility-sparing treatment, showing initial response in 98.7% of treated patients, progression in 10.8%, final complete response in 77.3%, recurrence in 29.8% and pregnancy in 21.1%.

Remarkably, TCR showed significantly higher rates of initial response than TCR+HT (98.7% vs 69.2%); no significant differences were found with respect to the other outcomes. In future studies, it would be interesting to assess whether the responsiveness of APA to progestins may be influenced by expression of certain molecules, as observed in endometrial hyperplasia and cancer.[18,19]

A possible advantage of TCR without HT over TCR+HT may be the shorter duration of the treatment, which allows attempts to conceive being starting earlier.

Based on our results and the adjunctive costs arising from the addition of HT to TCR, there seem to be limited evidence to recommend the addition of HT to TCR in the conservative treatment of APA.

However, the TCR techniques adopted differed among the included studies and showed different results. In our analysis, the best results

Premenopausal, n (%)	Cycle irregularity, n (%)	Nulliparity, n (%)	Infertility, n (%)	Symptoms (%)	Other pathologies (%)
18 (100)	7 (38.8)	18 (100)	-	-	-
22 (48.8)	-	5 (11.6)	3 (7.0%)	36 menorrhagia; 4 secondary anemia; 3 asymptomatic	8 diabetes mellitus; 13 hypertension; 1 hyperthyroidism; 9 uterine leiomyomas; 7 uterine glandular myopathy; 4 history of endometrial polyps; 1 history of breast cancer
-	11 (31.4)	35 (100)	1 (2.9)	24 hypermenorrhea; 5 metrorrhagia; 1 amenorrhea; 1 asymptomatic; 1 unknown	-
-	-	7 (70)	9 (90)	2 hypermenorrhea; 2 metrorrhagia; 2 pelvic mass; 1 irregular uterine bleeding; 1 menostaxis; 1 secondary infertility; 1 vaginal bleeding	2 ovarian cysts; 1 uterine adenomyoma; 1 uterine leiomyomas; 1 hypertension; 1 diabetes; 1 polycystic ovarian syndrome; 1 tubal pregnancy; 1 multiple endometrial polyps
8 (88.9)	-	1.0 ± 1.1child	2 (22.2)	5 abnormal uterine bleeding; 2 none	-
18 (100)	7 (38.8)	18 (100)	3 (16.7)	10 abnormal uterine bleeding; 1 vaginal discharge; 1 dysmenorrhea	-
27 (93.1)	11 (37.9)	22 (75.9)	6 (35.3)	8 hypermenorrhea; 8 dysmenorrhea	1 hypertension; 4 history of ovarian tumor; 6 anemia
53 (96)	-	28 (51)	15 (27.3)	most common: abnormal uterine bleeding less common: vaginal discharge, pelvic pain, postcoital spotting	1 history of breast cancer; 1 sclerocystic ovaries; 2 endometriosis; 1 ovarian serous cystadenoma; 1 diabetes mellitus; 1 acromegaly; 7 uterine leiomyomas
6 (100)	-	6 (100)	-	6 abnormal uterine bleeding	1 history of uterine tuberculosis; 1 uterine leiomyomas
26 (96.3)	-	10 (37)	3 (11.1)	24 abnormal uterine bleeding; 1 vaginal discharge; 1 asymptomatic	2 Turner's syndrome; 1 endometriosis
5 (100)	-	3 (60)	-	5 abnormal uterine bleeding	2 hypertension; 2 diabetes; 1 uterine leiomyomas
165/192 (85.9)	29/82 (35.4)	134/213 (62.9)	42/226 (18.6)	51/182 (28) abnormal uterine bleeding; 36/182 (19.8) menorrhagia 34/182 (18.7) hypermenorrhea	19/175 (10.9) uterine leiomyomas 13/175 (7.4) hypertension 12/175 (6.9) diabetes mellitus

were found in the study of Ma et al.[14] In that study, the TCR technique was performed in 4 steps according to Di Spiezio Sardo et al[20,21]: resection of APA (step 1); removal of 3-4 mm of endometrium adjacent to the lesion (step 2); removal of 2-3 mm of myometrium underlying the lesion (step 3); multiple random endometrial biopsies (step 4). Such a technique may also have the advantage of exploring the remaining endometrium with the random biopsies better, in order to exclude the presence of coexistent atypical hyperplasia and cancer. These conditions should indeed have priority in directing the management. Thus, based on the available evidence, TCR technique in 4 steps might be the optimal fertility-sparing treatment for women with APA.

It would be interesting to assess whether rates of progression and recurrence may be affected by pregnancy. Among patients who achieved pregnancy, only 1 case of recurrence and 1 of persistent disease were reported.[6,13] These findings seem to be in accordance with other studies that advocated a protective role of pregnancy on APA. In fact, Nomura et al[8] reported a significant inverse correlation between pregnancy and hysterectomy on multivariate analysis.[8] However, there are too few data to draw conclusions. We hope further studies will help in investigating this aspect.

Great uncertainty exists even regarding the follow up of patients diagnosed with APA. In fact, both modality and timing of follow up

TABLE 2 Characteristics of atypical polypoid adenomyoma

Study (Ref)	Specimen type	Lesion localization (%)			Mean size in mm (range)	Association with (%)				
		Fundus	Lower segment	Cervix		Hyperplasia without atypia	Atypical hyperplasia	Endometrial cancer	Other cancer	Adenomyosis
Nomura et al[9]	D&C	-	-	-	-	-	-	-	-	-
Ma et al[14]	-	27 (69.2)	8 (20.5)	4 (10.3)	20 (5-70)	2 at R	0	3 (7)	3 (6.9) ovarian cancer	-
Chiyoda et al[7]	Hysteroscopy	16 (45.7)	9 (25.7)	5 (14.3)	22 (9-51)	5 (14.3) 1 at third R (2.9)	2 (5.7) 2 at R (5.7) 1 at second R (2.9) 1 at fourth R (2.9)	1 at R (2.9) 3 at second R (8.6) 1 at third R (2.9)	0 (0)	-
Chen et al[13]	D&C	7 (70)	3 (30)	0 (0)	(15-50)	1 (10) 1 (10) during follow up	4 (40) 2 (20) during follow up	0 (0)	0 (0)	-
Grimbizis et al[12]	Histeroscopy	-	-	-	<20	0	2 (22.2)	1 (11.1)	0 (0)	-
Nomura et al[8]	D&C	-	-	-	-	0	1 (5.6)	4 (22.2)	0 (0)	-
Matsumoto et al[11]	-	17 (58.6)	10 (34.5)	2 (6.9)	23 (5-65)	0	1 (3.4)	5 (17.2)	0 (0)	
Longacre et al[6]	40 (72.2) D&C 7 (12.7) Hysteroscopy 7 (12.7) Hysterectomy 1 (1.8) Cervical polypectomy	16 (48.5)	11 (33.3)	1 (3)	18 (7-50)	2 (3.6) 1 at R (1.8)	1 (1.8) 1 at R (1.8)	0 (0)	1 unilateral ovarian endometrioid carcinoma 1 bilateral ovarian endometrioid carcinoma	4 (7.3)
Fukunaga et al[10]	3 (50) D&C 1 (16.7) Hysterectomy 2 (33.3) Hysteroscopy	1 (16.7)	2 (33.3)	3 (50)	15.2 (10-20)	0 (0)	1 (16.7) during follow up 1 at R (16.7)	1 (16.7)	0 (0)	-
Young et al[5]	22 (81.5) D&C 1 (3.7) Hysterectomy 2 (7.4) HBSO 2 (7.4) Cervical polypectomy	3 (21.4)	8 (57.1)	3 (21.4)	19 (1-60)	0 (0)	2 (7.4) 1 (3.7) during follow up	0 (0)	0 (0)	13 (48.1)
Mazur[1]	D&C	-	-	-	15 (7-30)	1 (20)	0 (0)	0 (0)	0 (0)	-
Total	98/165 (59.4) D&C 53 (32.1) Hysteroscopy 9 (5.5) Hysterectomy 3 (1.8) Cervical polypectomy 2 (1.2) HBSO	87/156 (55.8)	51/156 (32.7)	18/156 (11.5)	(1-70)	9/237 (3.8) 1 during follow up (.4) 3 at R (1.3) 1 at third R (.4)	13/237 (5.5) 4 at R (1.7) 1 at second R (.4) 1 at fourth R (.4) 3 during follow up (1.3)	14/237 (5.9) 1 at R (.4) 3 at second R (1.3) 1 at third R (.4)	5 (2.1) ovarian cancer	17/82 (20.7)

D&C, dilation and curettage; HBSO, hysterectomy and bilateral salpingo-oophorectomy; R, recurrence, -, not reported;.

TABLE 3 Characteristics of treatment and follow up

Study (Ref)	Treatment sample (%)		Treatment details	Follow-up time mean in months (range)	Follow-up type	Lost to follow up (%)
	Conservative	Non-conservative				
Nomura et al[9]	18/18 (100) HT 5/14 (35.7) HT+M	0 (0)	MPA (200-600 mg/d) with low-dose aspirin (100 mg/d) At 6 mo: CR or PR -> MPA discontinued; P-> MPA continued for 3 mo P at 9 mo -> hysterectomy or close observation; R -> hysterectomy or MPA	6.7 (22-179)	D&C or hysteroscopic biopsy and transvaginal ultrasonography every 3 mo during hormonal therapy for 2 y; every 4-6 mo for another 3 y, and once a year thereafter	0 (0)
Ma et al[14]	34/43 (79.1) TCR	5 (11.6) HBSO 1 (2.3) Hy 3 (7.0) Primary cytoreductive surgery	TCR in 4 stages according to Di Spiezio Sardo et al[17]	26.9 (2-57)	Transvaginal ultrasonography every 3-6 mo. Hysteroscopic biopsy in case of abnormal ultrasound findings	1 (2.3)
Chiyoda et al[7]	35/35 (100) TCR	0 (0)	TCR: 1-step hysteroscopic resection followed by IUD to prevent intrauterine adhesions. One 1 mo after, early second-look hysteroscopy with IUD removal	34.0 (4.2-133.7)	Cytology and ultrasonography at 4-6 mo after each TCR. If result was suspicious or positive, after a diagnostic hysteroscopy, another TCR	2 (5.7)
Chen et al[13]	10/10 (100) TCR+HT	0 (0)	TCR+HT: polypectomy under hysteroscopy followed by long-term progestin therapy (100 mg of MPA or 80 mg of megestrol acetate) for at least 3 mo. The patients subsequently attempted to conceive	- (19-145)	Curettage was carried out every 3 mo during the period of hormone therapy	0 (0)
Grimbizis et al[12]	9/9 (100) TCR	0 (0)	Hysteroscopic removal of the lesion with additional endometrial curettage at the end of the procedure	120 (50.4-189.6)	Bimanual clinical examination, Papanicolaou smear test, and 2-dimensional transvaginal sonogram every year. Hysteroscopic biopsy if: (a) abnormal ultrasound findings, (b) abnormal uterine bleeding, (c) endometrial hyperplasia	0 (0)
Nomura et al[8]	18/18 (100) HT 5/14 (35.7) HT+M	0 (0)	MPA (200-600 mg/d) with low-dose aspirin (100 mg/d) At 6 mo: CR or PR -> MPA discontinued; P-> MPA continued for 3 mo P at 9 mo -> hysterectomy or close observation; R -> hysterectomy or MPA	77.7 (22-142)	D&C or hysteroscopic biopsy and transvaginal ultrasonography every 3 mo during hormonal therapy for 2 y; every 4-6 mo for another 3 y, and once a year thereafter	0 (0)

TABLE 3 (continued)

Study (Ref)	Treatment sample (%)		Treatment details	Follow-up time mean in months (range)	Follow-up type	Lost to follow up (%)
	Conservative	Non-conservative				
Matsumoto et al[11]	9/29 (31) D&C 2/29 (6.9) vaginal resection 10/29 (34.5) TCR	8/29 (27.6) Hy	-	39.6 (1-202)	-	0 (0)
Longacre et al[6]	29/48 (60.4) TCR+HT	19/48 (39.6) Hy 7/55 (12.7) Hy for other indications	Polypectomy followed by progestational agent	25.2 (1-112)	-	2 (3.6)
Fukunaga et al[10]	2/5 (40) D&C+HT 1/5 (20) TCR	1/5 (20) Hy 1/5 (16.7) chemotherapy for coexisting EC 1/6 (16.7) Hy for other indication	-	13.5 (4-42)	D&C; timing not specified	0 (0)
Young et al[5]	6/22 (27.3) D&C 2/22 (9.1) TCR	15/27 (55.6) Hy; 1/27 (3.7) for other indications 2/27 (7.4) HBSO for other indications 1/27 (3.7) Hy + radiotherapy (misinterpreted as carcinoma) 1/27 (3.7) HBSO + radiotherapy (misinterpreted as carcinoma)	-	- (12-276)	D&C; timing not specified	5 (18.5)
Mazur[1]	2/5 (40) D&C	2/5 (40) Hy 1/5 (20) Hy + chemotherapy (misinterpreted as carcinosarcoma)	-	15.2 (4-24)	-	0 (0)
Total	169 91 (53.8) TCR 39 (23.1) TCR+HT 18 (10.7) HT 17 (10.1) D&C 2 (1.2) D&C+HT 2 (1.2) vaginal resection	58 44 (75.8) Hy; 9 (15.5) for other indications 7 (12) HBSO; 2 (3.4) for other indications 3 (5.2) Primary cytoreductive surgery 1 (1.7) chemotherapy for coexisting EC 1 (1.7) Hy + radiotherapy (misinterpreted as carcinoma) 1 (1.7) HBSO + radiotherapy (misinterpreted as carcinoma) 1 (1.7) Hy + chemotherapy (misinterpreted as carcinosarcoma)	-	- (1-276)	-	-

CR, complete response; D&C, dilation and curettage; HBSO, hysterectomy and bilateral salpingo-oophorectomy; HT, hormonal therapy; Hy, hysterectomy; M, MPA maintenance; P, persistence; PR, partial response; R, recurrence; TCR, hysteroscopic transcervical resection; -, not reported.

TABLE 4 Oncologic outcomes of fertility-sparing treatments

Study (Ref)	Treatment	Oncologic outcomes of conservative treatment (%)				Persistence and subsequent treatment	Progression (%)	Final CR (%)	Final hysterectomy (%)	Time to hysterectomy in months (range)
		CR	PR	P	LOST					
Nomura et al[9]	HT	14/18 (77.8) [of whom 5 M]		4/18 (22.2)	0 (0)	2/4 HT -> hy 2/4 (50) hy	1M(R)/5M (20) 9/13 (69.2)	4/5 M (80) 2/13 (15.4)	1/5 M (20) 11/13 (84.6)	44.7 (19-84)
Ma et al[14]	TCR	30/30 (100)	0 (0)	0 (0)	0 (0)	0	0/30 (0)	25/30 (83.3)	5/30 (16.7)	-
Chiyoda et al[7]	TCR	33/35 (94.3)	1/35 (2.9)	0/35 (0)	1/35 (2.9)	-	7/35 (20)	26/35 (74.3)	9/35 (25.7)	-
Chen et al[13]	TCR+HT	9/10 (90)	0 (0)	1/10 (10)	0 (0)	0	1(R)/10 (10) 1 (not reported)/10 (10)	8/10 (80)	2/10 (20)	-
Grimbizis et al[12]	TCR	9/9 (100)	0 (0)	0 (0)	0 (0)	0	1(R)/9 (11.1)	6/9 (66.6)	3/9 (33.3)	(36-50) -
Nomura et al[8]	HT	7/18 (38.9)	7/18 (38.9)	4/18 (22.2)	0 (0)	2/4 HT -> hy 2/4 (50) hy	9 (50)	6/18 (33.3)	12/18 (66.6)	40.3 (24-68)
Matsumoto et al[11]	D&C Vaginal resection TCR	-	-	-	-	-	-	-	-	-
Longacre et al[6]	TCR+HT	18/29 (65.5)	0 (0)	11/29 (37.9)	0 (0)	8/11 (72.7) HT 1/11 (9.1) HT -> hy 2/11 (18.2) hy	0 (0)	24/29 (82.8)	5/29 (17.2)	22.6 (5-40)
Fukunaga et al[10]	D&C+HT TCR	1/2 (50) D&C+HT; 1/1 (100) TCR	0 (0)	1/2 (50) D&C+HT; 0/0 (0) TCR	0 (0)	1 D&C+HT	-	3/3 (100)	0/3 (0)	-
Young et al[5]	D&C TCR	4/6 D&C (66.7); 2/2 TCR (100)	0 (0)	2/6 (33.3) D&C; 0/0 (0) TCR	0 (0)	-	-	-	-	-
Mazur[1]	D&C	2/2 (100)	0 (0)	0 (0)	0 (0)	-	0 (0)	2/2 (100)	0/2 (0)	-
Total	All treatments	123/143 (86)		19/143 (13.3)	1/143 (.7)	11/19 (57.9) HT 4/19 (21.1) hy 1/19 (5.3) D&C+HT	29 [of whom 2 R]/175 (16.6)	112/162 (69.1)	48/154 (31.2)	(5-84)
	HT	14/18 (77.7)		4/18 (22.2)	0		1M (R)/5M (20) 9/13 (69.2)	4/5 M (80) 2/13 (15.4)	1/5 M (20) 11/13 (84.6)	(19-84)
	TCR	75/76 (98.7)		0/76 (0)	1/76 (1.3)		8 [of whom 1R]/74 (10.8)	58/75 (77.3)	17/75 (22.7)	(36-50)
	TCR+HT	27/39 (69.2)		12/39 (30.8)	0		2 [of whom 1R]/39 (5.1)	32/39 (82.1)	7/39 (17.9)	(5-40)
	D&C	6/8 (75)		2/8 (25)	0		0/2 (0)	2/2 (100)	0/2 (0)	-
	D&C+HT	1/2 (50)		1/2 (50)	0		-	2/2 (100)	0/2 (0)	-

CR, complete response; D&C, dilation and curettage; HBSO, hysterectomy and bilateral salpingo-oophorectomy; HT, hormonal therapy; Hy, hysterectomy; M, patients with MPA maintenance; P, persistence; PR, partial response; R, patient who had recurrence of APA; TCR, hysteroscopic transcervical resection; -, not reported.

TABLE 5 Reproductive outcomes of fertility-sparing treatment

		Pregnancies	
Study (Ref)	**Treatment**	**Total (%)**	**Details**
Nomura et al[9]	HT	2/5M (40) 2/13 (15.4)	-
Ma et al[14]	TCR	-	-
Chiyoda et al[7]	TCR	6/35 (17.1)	1 patient conceived after a first recurrence treated by TCR and 1 after a third recurrence treated by a fourth TCR 4 patients had normal vaginal delivery and 1 cesarean delivery owing to a fetal condition Details about 1 women were not reported because pregnancy occurred at the last follow up
Chen et al[13]	TCR+HT	7/10 (70)	1 patient conceived 2 times: 1 natural delivery and 1 twin pregnancy with cesarean section; 3 patients had term delivery with natural conception 5 patients underwent in vitro fertilization and embryo transfer (IVF-ET): 2 failed, while 3 had a cesarean delivery at 21, 37 and 50 mo 2 of 3 non-pregnant patients were relatively older, and another was a recent case
Grimbizis et al[12]	TCR	2/3 (66.6)	3 patients stated that they did not completed their family: 1 patient had a delivery 6 y after the initial diagnosis, 1 had a delivery 1 y after the initial diagnosis by intrauterine insemination, and 1 was under consideration for using assisted reproduction techniques
Nomura et al[8]	HT	4/18 (22.2)	5 patients tried to conceive: 3 conceived spontaneously and 1 conceived 2 times (the first one with clomiphene and the second one spontaneously)
Matsumoto et al[11]	D&C Vaginal resection TCR	-	-
Longacre et al[6]	TCR+HT	5/29 (17.2)	5 patients with recurrent or persistent lesions subsequently became pregnant and delivered normal full-term infants, including one patient who bore two children
Fukunaga et al[10]	D&C+HT TCR	-	-
Young et al[5]	D&C TCR	-	-
Mazur[1]	D&C	1/5 (20)	-
Total	All treatment	24/95 (25.3)	-
	HT	2/5M (40) 2/13 (15.4)	
	TCR	8/38 (21.1)	
	TCR+HT	12/39 (30.8)	
	D&C	-	
	D&C+HT	-	

CR, complete response; D&C, dilation and curettage; HBSO, hysterectomy and bilateral salpingo-oophorectomy; HT, hormonal therapy; Hy, hysterectomy; M, MPA maintenance; P, persistence; PR, partial response; R, recurrence; TCR, hysteroscopic transcervical resection; -, not reported.

were different among the studies. In three studies,[8,9,13] D&C or hysteroscopic specimens were obtained only in the case of suspicious findings on ultrasonography, whereas in the other studies, histological examination was performed at every follow-up visit. Given the risk of recurrence, progression and coexistent atypical hyperplasia and/or cancer, we think that a close follow up based on histological examination would be advisable.

The interval between follow-up visits ranged from 3 months to 1 year. It should be noted that up to four recurrences, with a disease-free interval up to 60 months, were described, and 1 patient needed to undergo hysterectomy 84 months after the beginning of the conservative treatment. Therefore, a long follow-up duration should be advisable. The follow-up modality described by Nomura et al appears to be a safe approach,[8,9] consisting of dilation and curettage or hysteroscopic biopsy plus transvaginal ultrasonography every 3 months for the first 2 years, every 4-6 months for another 3 years, and once a year thereafter.[8,9]

In one study, tumor markers CA125 and CA19.9 were also assessed, reporting normal values[7]; however, evidence for their use is lacking. Instead, it is possible that some markers associated with

TABLE 6 Comparison of transcervical resection techniques

Study (Ref)	Technique	Oncologic outcomes of conservative treatment (%)				Progression (%)	First recurrence (%)	Final CR (%)	Final hysterectomy (%)	Pregnancies (%)
		CR	PR	P	LOST					
Ma et al[14]	4 stages according to Di Spiezio Sardo et al[17]	30/30 (100)	0 (0)	0 (0)	0 (0)	0/30 (0)	3/30 TCR (10)	25/30 (83.3)	5/30 (16.7)	-
Chiyoda et al[7]	1-step hysteroscopic resection + IUD insertion. Second-look hysteroscopy with IUD removal after 1 mo	33/35 (94.3)	1/35 (2.9)	0/35 (0)	1/35 (2.9)	7/35 (20)	19/35 (54.3)	26/35 (74.3)	9/35 (25.7)	6/35 (17.1)
Grimbizis et al[12]	Hysteroscopic removal of the lesion with additional endometrial curettage at the end of the procedure	9/9 (100)	0 (0)	0 (0)	0 (0)	1R/9 (11.1)	2/9 (22.2)	6/9 (66.6)	3/9 (33.3)	2/3 (66.6)
Matsumoto et al[11]	-	-	-	-	-	-	-	-	-	-
Fukunaga et al[10]	-	1/1 (100)	0 (0)	0/0 (0)	0 (0)	-	0/2 TCR (0)	3/3 (100)	0/3 (0)	-
Young et al[5]	-	2/2 (100)	0 (0)	0/0 (0)	0 (0)	-	-	-	-	-

-, not reported.

premalignant endometrial hyperplasia or endometrial cancer might also be useful in the diagnosis and risk stratification of APA, as these two lesions share several molecular features.[22-26]

To the best of our knowledge, this study is the first quantitative systematic review about APA. We aimed to determine the optimal treatment and follow up for this lesion, which is still not standardized. Moreover, we tried to improve the quality of evidence about clinicopathologic characteristics and behavior of APA, as well as the risks of cancer and recurrence.

Limitations to our results might be the retrospective design of the included studies, the relatively small sample size and the lack of studies that compares different treatments. Such limitations particularly affect comparisons among TCR techniques. However, given the rarity of APA, prospective large studies are difficult to perform. To date, evidence driving the management of APA has been based on case reports and small retrospective case series.

Our systematic review with non-weighted quantitative synthesis of the data may provide the first statistical evidence in this field, and may represent a step towards an evidence-based standardization of the management of APA.

5 | CONCLUSION

Given the risk of recurrence and progression, APA might be treated by hysterectomy in patients with no desire for pregnancy. Since most patients are premenopausal, a fertility-sparing treatment is necessary. TCR may be considered the first-line fertility-sparing treatment, as it showed superiority all other conservative approaches in terms of both effectiveness and safety. In particular, the 4-step TCR described by Di Spiezio Sardo et al[14,17] showed the best results. The follow up might be based on transvaginal ultrasonography and histological examination every 3 months for the first 2 years, every 4-6 months for another 3 years, and once a year thereafter.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ORCID

Antonio Raffone https://orcid.org/0000-0001-5443-2333

Antonio Travaglino https://orcid.org/0000-0003-4002-1618

Gabriele Saccone https://orcid.org/0000-0003-0078-2113

REFERENCES

1. Mazur MT. Atypical polypoid adenomyomas of the endometrium. *Am J Surg Pathol*. 1981;5:473-482.
2. Jiang QY, Wang L, Wu RJ. A multiple perspectives on atypical polypoid adenomyoma of uterus. *Gynecol Endocrinol*. 2013;29(7):623-625.
3. Heatley MK. Atypical polypoid adenomyoma: a systematic review of the English literature. *Histopathology*. 2006;48(5):609-610.

4. McCluggage WG. A practical approach to the diagnosis of mixed epithelial and mesenchymal tumours of the uterus. *Mod Pathol*. 2016;29(suppl 1):S78-S91.
5. Young RH, Treger T, Scully RE. Atypical polypoid adenomyoma of the uterus. A report of 27 cases. *Am J Clin Pathol*. 1986;86(2):139-145.
6. Longacre TA, Chung MH, Rouse RV, et al. Atypical polypoid adenomyofibromas (atypical polypoid adenomyomas) of the uterus. A clinicopathologic study of 55 cases. *Am J Surg Pathol*. 1996;20(1):1-20.
7. Chiyoda T, Lin BL, Saotome K, et al. Hysteroscopic transcervical resection for atypical polypoid adenomyoma of the uterus: a valid, fertility-preserving option. *J Minim Invasive Gynecol*. 2018;25(1):163-169.e1.
8. Nomura H, Sugiyama Y, Tanigawa T, et al. Long-term outcomes of fertility-sparing treatment of atypical polypoid adenomyoma with medroxyprogesterone acetate. *Arch Gynecol Obstet*. 2016;293(1):177-181.
9. Nomura H, Sugiyama Y, Tanigawa T, et al. Maintenance hormonal therapy after treatment with medroxyprogesterone acetate for patients with atypical polypoid adenomyoma. *Jpn J Clin Oncol*. 2018;48(3):255-258.
10. Fukunaga M, Endo Y, Ushigome S, et al. Atypical polypoid adenomyomas of the uterus. *Histopathology*. 1995;27(1):35-42.
11. Matsumoto T, Hiura M, Baba T, et al. Clinical management of atypical polypoid adenomyoma of the uterus. A clinicopathological review of 29 cases. *Gynecol Oncol*. 2013;129(1):54-57.
12. Grimbizis GF, Mikos T, Miliaras D, et al. Management of atypical polypoid adenomyomas. A case series. *Eur J Obstet Gynecol Reprod Biol*. 2017;215:1-5.
13. Chen Q, Lu W, Lu B. Pregnant outcomes of atypical polypoid adenomyoma treated with progestin therapy. *J Obstet Gynaecol Res*. 2018;44(2):323-330.
14. Ma B, Zhu Y, Liu Y. Management of atypical polypoid adenomyoma of the uterus: a single center's experience. *Medicine (Baltimore)*. 2018;97(12):e0135.
15. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
16. Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73(9):712-716.
17. Travaglino A, Raffone A, Saccone G, et al. Endometrial hyperplasia and risk of coexistent cancer: WHO vs EIN criteria. *Histopathology*. 2018. https://doi.org/10.1111/his.13776. [Epub ahead of print]
18. Zakhour M, Cohen JG, Gibson A, et al. Abnormal mismatch repair and other clinicopathologic predictors of poor response to progestin treatment in young women with endometrial complex atypical hyperplasia and well-differentiated endometrial adenocarcinoma: a consecutive case series. *BJOG*. 2017;124(10):1576-1583.
19. Travaglino A, Raffone A, Saccone G, et al. PTEN as a predictive marker of response to conservative treatment in endometrial hyperplasia and early endometrial cancer. A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:104-110.
20. Di Spiezio Sardo A, Mazzon I, Gargano V, et al. Hysteroscopic treatment of atypical polypoid adenomyoma diagnosed incidentally in a young infertile woman. *Fertil Steril*. 2008;89(2):456.e9-456.e12.
21. Giampaolino P, Di Spiezio Sardo A, Mollo A, et al. Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: a retrospective study. *J Minim Invasive Gynecol*. 2018;pii: S1553-4650(18)30347-9. https://doi.org/10.1016/j.jmig.2018.07.001. [Epub ahead of print]
22. Yen TT, Miyamoto T, Asaka S, et al. Loss of ARID1A expression in endometrial samplings is associated with the risk of endometrial carcinoma. *Gynecol Oncol*. 2018;150(3):426-431.
23. Travaglino A, Raffone A, Saccone G, et al. Immunohistochemical nuclear expression of β-catenin as a surrogate of CTNNB1 exon 3 mutation in endometrial cancer. *Am J Clin Pathol*. 2019. https://doi.org/10.1093/ajcp/aqy178. [Epub ahead of print]
24. Raffone A, Travaglino A, Saccone G, et al. Loss of PTEN expression as diagnostic marker of endometrial precancer: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2018. https://doi.org/10.1111/aogs.13513. [Epub ahead of print]
25. Raffone A, Travaglino A, Saccone G, et al. PAX2 in endometrial carcinogenesis and in differential diagnosis of endometrial hyperplasia. A systematic review and meta-analysis of diagnostic accuracy. *Acta Obstet Gynecol Scand*. 2018. https://doi.org/10.1111/aogs.13512. [Epub ahead of print]
26. Travaglino A, Raffone A, Saccone G, et al. Loss of B-cell lymphoma 2 immunohistochemical expression in endometrial hyperplasia: a specific marker of precancer and novel indication for treatment: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2018;97(12):1415-1426.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Raffone A, Travaglino A, Saccone G, et al. Management of women with atypical polypoid adenomyoma of the uterus: A quantitative systematic review. *Acta Obstet Gynecol Scand*. 2019;00:1-14. https://doi.org/10.1111/aogs.13553